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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/599,271	10/01/90	SULLIVAN	THER-0026

EXAMINER	
SCHWADRON, R	
ART UNIT	PAPER NUMBER
1811	9

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DATE MAILED: 03/23/93

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents and Trademarks

Responsive to Communication Filed _____ .

The enclosed is a correct copy of a reference relating to the last Office action. The correction is indicated below.

THE PERIOD FOR RESPONSE OF 3 MONTHS SET IN SAID OFFICE ACTION IS RESTARTED TO BEGIN WITH THE DATE OF THIS LETTER.

☑ Part 1 - Correct Reference Citation

Remailed Office action dated 3-1-93

by Donna Chapman
Examiner

☐ Part 2 - Correct Reference Furnished:

_____

_____

by _____
Reference Order Center

enc.

15. Claims 20-30 are pending in the instant application.

16. This application does not contain an Abstract of the Disclosure as required by 37 C.F.R. § 1.72(b). An Abstract on a separate sheet is required.

17. Applicant should update the status of the parent cases of the instant application.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately make and/or use the invention i.e. failing to provide an enabling disclosure.

A) Applicant has not disclosed the claimed antivenin composition as useable for human administration. While applicant speculates that anaphylaxis problems with the purified antivenin composition may be reduced no evidence to support this notion is provided. In fact, no information is provided indicating whether the antivenin preparations are suitable for use in humans with regards to toxicity from contaminants related to the purification of these antibodies or with regards to anaphylactic problems related to the administration of these reagents to humans. Therefore the specification is not enabling for claims related to

the antivenin composition of the instant invention.

B) Applicant has not disclosed $F(ab)_2$ fragments extracted from any antibody containing source using the process of the instant invention. Goding et al. teach (page 131, first line) that is not possible to find suitable conditions for the production of $F(ab)_2$ fragments from mouse IgG2b using pepsin digestion. Furthermore, Goding describes that specific conditions and buffers are necessary to yield pepsin treatment derived $F(ab)_2$ fragments from other mice IgG subclasses. Goding also describes various specific treatments (pages 131-132) necessary to render various rat IgG subclasses susceptible to $F(ab)_2$ generation by pepsin treatment. None of this specific information is taught in the specification. Therefore the specification fails to enable the instant invention.

(C) Applicant has not sufficiently disclosed the purity of the purified IgG molecules or fragments purified using the instant invention. There is no indication of the specific sensitivity of the immunoelectrophoresis method used to allegedly demonstrate the immunoelectrophoresis method used to allegedly demonstrate the purity of antibody or antibody fragment preparations purified using the instant invention. Therefore, the various antibodies or fragments thereof may contain contamination when analyzed for the presence of Fc fragments or extraneous Ig class molecules which are present and could be detected by a more sensitive state of the art technique such as quantitative ELISA. ELISA assays can detect picogram quantities of antigen when the assay system is maximally configured. Therefore the specification is not

enabling for $F(ab)_2$ fragment of F(ab) fragment or IgG molecule purified using the process of he instant invention because the purity of said antibodies or fragments thereof has not been determined using state of the art techniques.

19. Claims 20-30 are rejected under 35 U.S.C. § 112, first paragraph for the reasons set forth in the objection to the specification.

20. Claim 29 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to an antivenin composition which specifically binds venom of the Crotalus genus. The specification is not enabling for F(ab) fragment antivenin against any toxin because the production of and efficacy of such an antivenin against a toxin other than Crotalus venom is not described in the specification. See M.P.E.P. §§ 706.03(n) and 706.03(z).

21. Claims 20-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 21 are indefinite in the recitation of "antibody containing source" because it is unclear what this encompasses. Claims 20-22 are indefinite in the readaptation of "subsequent recovery" because it is unclear from where and when the fragments or antibodies are recovered. Insertion of "from the matrix" or an equivalent phrase following "recovery" is suggested. Claim 23 and 25 are indefinite in the recitation of "polyvalent IgG(T)" because it is unclear what this means.

Claims 24 and 26 are indefinite in the recitation of "polyvalent anti-horse serum" because it s unclear whether this is a polyvalent horse specific antisera or polyvalent antiserum made in a horse against a specific antigen. Claims 27-30 are indefinite in the recitation of "active against". "Specifically binds " is a preferred substitution. Claims 27-29 are indefinite in the recitation of "produce an electrophoresis" because it is unclear what this means. Claims 27-30 are indefinite in the recitation of "molecular ~~wight~~ weight" with out giving details of the assay used to ascertain said molecular wight. Claims 27 and 29 are indefinite in the recitation of "showing that anti-$F(ab)_2$ materials give a precipitation band against F(ab) fragments but produce no precipitation band against anti-F(c) materials" because the meaning of this phrase is incomprehensible. Claims 27 and 22 are indefinite in the recitation of "bulk antibody source" because it is unclear what this "bulk antibody" is or what its source is. In claims 20 and 21 it is suggested that the parenthesises be removed form the phrase "(having an affinity for...) because it is unclear whether applicant intends to delete this or not. Brackets are appropriate if deletion is intended.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22, 30 are rejected under 35 U.S.C. § 102(b) as being

clearly anticipated by Sullivan et al.

Sullivan et al. teaches an antivenin composition (consisting of IgG molecules) purified from a bulk antibody containing source by affinity chromatography with an antigen (snake venom) embedded in a polyacrylamide matrix (see entire document).

23. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

24. Claims 27-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Stanworth et al.

The claims are drawn to F(ab) or $F(ab)_2$ antivenin compositions. Sullivan et al. teaches an antivenin composition consisting of IgG molecules. Stanworth et al. teaches production of F(ab) or $F(ab)_2$ Ig fragments by digestion with papain (to produce F(ab)) or pepsin (to produce $F(ab)_2$). Stanworth et al. also teach that "the absence of most of the ~~fc~~ Fc immunogenic determinants has led to the use of $F(ab)_2$ fragments in various clinical contexts. For example, $F(ab)_2$ fragments ~~form~~ from horse antitoxin and horse anti-lymphocyte globulin have been preferred

to the whole antibody molecule which may sensitize the r cipient to horse ~~fc~~ Fc determinants" (page 6.19, last paragraph). It would have been prima facie obvious to one of ordinary skill in the art to produce antivenin compositions consisting of F(ab) or $F(ab)_2$ because Sullivan et al. teaches an antivenin IgG composition, Stanworth teaches the production of F(ab) or $F(ab)_2$ fragments from IgG and the reduced immunogenicity of such compositions due to the absence of Fc determinants. It would have been obvious to a routineer that these antivenin compositions containing F(ab) or $F(ab)_2$ fragments would have been produced against crotalus venom (as described by Sullivan et al.) or any other venom. One of ordinary skill in the art would have been motivated to do the aforementioned in order to reduce the immunogenicity of antivenin compositions by removing Ig Fc determinants. A routineer would have a reasonable expectation of success because Sullivan et al. describes an IgG antivenin composition, Stanworth et al. describes the production of F(ab) or $F(ab)_2$ fragments and the motivation for doing so.

25. Claims 20, 21, 23-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Smith et al. in view of Sullivan et al. and Bernfeld et al.

The claims are drawn to F(ab) or $F(ab)_2$ fragments extracted from an antibody containing source by sequential treatment with a papain polyacrylamide matrix or pepsin polyacrylamide matrix and affinity chromatography with an antigen polyacrylamide matrix. Smith et al. teach F(ab) fragments purified by affinity chromatography (see entire document). Smith et al. do not teach

that the antigen or enzyme (papain or pepsin) was embedded in polyacrylamide. Sullivan et al. teach antigen embedded polyacrylamide for affinity chromatography of horse antisera to purify Ig specific for snake venom. (See entire document). Bernfeld et al. teach enzymes immobilized in polyacrylamide including papain (see page 678. table 1). It would have been prima facie obvious to one of ordinary skill in the art to purify F(ab) fragments using polyacrylamide immobilized antigen and polyacrylamide immobilized papain because Smith teaches F(ab) fragments purified by affinity chromatography, Sullivan teaches affinity chromatography with polyacrylamide immobilized antigen and Bernfeld teaches papain immobilized in polyacrylamide. It also would have been obvious that $F(ab)_2$ fragments could be purified using the same protocol except for substituting pepsin in the polyacrylamide matrix. One of ordinary skill in the art would be motivated to do the aforementioned because polyacrylamide gel immobilization overcomes some of the problems associated with other means of antigen or enzyme immobilization (as detailed by Bernfeld in the last sentence of paragraph 1, page 678). It would have been obvious to use this procedure to obtain F(ab) or $F(ab)_2$ fragments from horse antiserum because Sullivan et al. teach horse antiserum as a source of antibodies in his reference (see entire document). IgG(T) is a component of horse antisera so it would have been obvious to purify it using the procedure of the instant invention. One would have been motivated to purify F(ab) or $F(ab)_2$ fragments from horse antisera or horse Ig(T) because Smith et al teach the reduced

immunogenicity of antibody fragments not containing the Fc region and clinical relevance of this finding (page 395, second paragraph). One of ordinary skill in the art would have a reasonable expectation of success because Smith et al teach F(ab) fragments isolated by affinity chromatography, Sullivan et al. teach affinity chromatography to purify antibodies from horse antigen using polyacrylamide immobilized antigen and Bernfeld teach polyacrylamide immobilized enzymes.

26. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

27. No claim is allowed.

28. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to group 180 via the PTO Center located in Crystal Mall 1. The facing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron whose telephone number is (703) 308-4680.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180

Ron Schwadron

Ron Schwadron, Ph.D/em
March 12, 1993